Commentary

Interactions of Viruses with Dendritic Cells: A Double-edged Sword

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Diverse mechanisms are used by viruses to inhibit, block, or evade the immune response (see review in reference 1). These include reduced expression of critical antigenic epitopes (e.g., EBV in latency), genetic variation of class I–restricted CTL epitopes (HIV-1), clonal exhaustion of CTLs (HIV-1, lymphocytic choriomeningitis virus), downregulation of MHC class I and peptide–MHC complex expression (HSV, adenovirus, cytomegalovirus), production of an immunosuppressive cytokine (e.g., IL-10–like factors by EBV), and downregulation of critical cytokines such as IL-12 (measles virus, HIV-1).

Three studies, two published in this issue of *The Journal of Experimental Medicine*, describe a new mechanism whereby virus infection can subvert the immune response (2–4). Measles virus (MV) infection induces dendritic cell (DC) apoptosis and syncytia formation, leading to profound inhibition of IL-12 production by DCs and T cell proliferation. These studies may therefore provide some explanation for the dramatic immunosuppression that is often observed during MV infection. In addition, they highlight the dual and contrasting roles of DCs as potentiators of antiviral immune responses versus facilitators of disease pathogenesis and immunosuppression.

Characteristics of MV Infection

MV is acquired through the respiratory epithelium where it replicates and disseminates throughout the lymphoid system (5). MV binds to a surface receptor, CD46, one of the regulators of complement activation via hemagglutinin (HA), and then fuses with the cell membrane via its fusion (F) protein (6). Syncytia or multinucleated giant cells (Warthin-Finkeldy cells) have been identified in the submucosal regions of the tonsils and pharynx (7), and may be a source of MV that spreads to other organs and tissues throughout the blood stream.

In healthy children, measles infection is generally self-limited, causing primarily a rash and fever. Complications include an otitis media, pneumonia, gastroenteritis, and rare central nervous system syndromes including a postinfectious encephalitis and a delayed subacute sclerosing panencephalitis (5). MV infection can be complicated by a period of immunosuppression that can lead to secondary infections by bacteria and fungi (8). This is especially significant in developing countries where malnutrition compounds the morbidity associated with these opportunistic infections. Marked and prolonged abnormalities of cell-mediated immunity have been described. They include T cell lymphocytopenia (9), inhibition of delayed-type hypersensitivity responses (10), suppression of recall responses or proliferation to mitogen or alloantigens (11, 12), suppression of antibody production (13), and cell cycle arrest of lymphoid cells in the G1 phase (11, 12). There may also be skewing of the T helper response towards the Th2 phenotype (14). Cell-mediated immunity appears to be critical in controlling measles infection. Both $CD4^+$ and $CD8^+$ cells have been implicated in the elimination of measles virus, but it is thought that the humoral response is required for reducing viral load (5).

MV Infects DCs. Several sources of DCs have been investigated: mature cells grown from cord blood progenitors in GM-CSF and TNF (3), skin Langerhans cells (3), mature circulating blood DCs (4), and immature DCs derived from blood monocytes exposed to GM-CSF and IL-4 (2). All DC sources were shown to be productively infected with MV, including the Halle and Edmonston strains. 40–100% of DCs infected at multiplicities of infection (MOIs) of 0.05–0.1 expressed the viral proteins HA and F. Infectious particles were produced, albeit at low levels, 2×10^3 PFU/10^6 DCs. A small proportion of DCs formed syncytia. However, DC integrity and viability became grossly compromised after a 3–4-d culture, secondary to apoptosis, with death approaching levels of 45–70%. All apoptotic APCs expressed nucleoprotein (NP; reference 2). Monocytes produced similar levels of infectious virus to DCs (peaking at day 5 after infection), and also died from apoptosis but did not form syncytia (2).

Enhancement of MV Production in DC–T Cell Cocultures. When MV-infected DCs were cocultured with T cells, a number of striking observations were made. First Fugier-Vivier et al. (2) showed that addition of PMA/ionomycin-activated T cells increased MV production in DCs up to 18-fold. In contrast, infection in monocytes was only increased 4-fold. Second, syncytia formation increased 7–15-fold. The effects were evident shortly (1–2 d) after DC–T cell coculture. Third, although viral replication occurred primarily in DCs (40–50% NP^+) versus T cells (10% NP^+), dramatic levels of apoptosis were evident in both APCs and T cells, leading to 90% cell death by 7 d of coculture. It is not known whether the apoptosis is secondary to the expression of TNF-R superfamily and their ligands, including fasL and fas, as described in HIV-1 infection (15).

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MV Interferes with DC and T Cell Function. All three studies demonstrated that T cell proliferation was markedly diminished in cocultures of MV-infected DCs and T cells. Fugier-Vivier et al. (2) found that the effect was evident early in the T cell response (1–2 d). The enhanced production of MV and syncytia formation induced in DCs upon contact with T cells was dependent upon CD40, as it could be significantly blocked by anti-CD40L Ab or mimicked with CD40L-transfected fibroblasts (2). Furthermore, IL-12 production by MV-infected DCs was abrogated by 70%. Since DCs are normally induced to synthesize IL-12 through CD40 signaling (16, 17), this suggests that independent pathways triggered by MV infection abrogate this effect. Indeed, it has recently been demonstrated that antibodies to CD46 can inhibit IL-12 production (18). Curiously, UV-irradiated MV partially inhibited cell proliferation (30%) and IL-12 production (20–30%), but did not induce apoptosis of DCs or T cells or syncytia formation (2).

Using a different system, Grosjean et al. (3) demonstrated that the ability of DCs to stimulate naive, $CD45RA^+$, $CD4^+$ T cells in the allogeneic mixed leukocyte reaction was completely abrogated after MV infection. As few as 30–100 infected cells caused substantial inhibition (>90%) of proliferation by 2×10^4 T cells. Only a 1-h contact was sufficient and, although there was progressive loss of DC viability, T cell viability was not compromised. These findings differ from Fugier-Vivier et al. (2) in that the latter observed extensive death of T cells. One reason for this may be that Grosjean et al. used mature DC populations. Mature DCs are less efficient at permitting HIV-1 replication than immature cells and may also be less permissive for MV (Granelli-Piperno, A., E. Delgado, V. Finkel, W. Paxton, and R. Steinman, manuscript submitted). Furthermore, these investigators used naive $CD45RA^+$ cells rather than preactivated cells.

MV Interferes with the Function of Other APCs. Some of the mechanisms postulated to account for MV-induced immunosuppression here have been described before, although with other cells and not DCs as APCs. For example, Schendler et al. (19) showed that proliferation of PBLs in response to a variety of stimuli was significantly impaired after cocultivation with MV-infected, UV-irradiated autologous blood lymphocytes or monocytes. Direct cell–cell contact rather than inhibition by direct virus infection or release of an inhibitory factor was required. Both the MV HA and F proteins appeared to be critical as coexpression of both, but not the individual proteins, in nonlymphoid cells was necessary to suppress T cell proliferation.

Karp et al. demonstrated that MV infection efficiently downregulated IL-12 production in primary human monocytes (18). Relatively few monocytes (<3% of the total number) needed to be productively infected with MV for inhibition of IL-12 production after stimulation with LPS or staphylococcus Cowan strain 1 plus IFN-γ. However, productive infection was not required for the effect, since pulsing with UV-inactivated MV also suppressed IL-12 synthesis. The mechanism of suppression was considered to be directly due to CD46 cross-linking, since incubation of CD46 with specific monoclonal antibodies or dimerized C3b directly blocked IL-12 production by LPS or staphylococcus Cowan strain 1 plus IFN-γ.

Finally, B cells also succumb to the effects of MV. In an earlier issue, Ravenel et al. (20) reported that recombinant MV NP directly binds to FcRγII on B cells and inhibits polyclonal Ig production by as much as 50%. Thus, MV appears to affect a multitude of cells and cellular functions that lead to suppression of both cell-mediated and humoral immunity.

Role of DCs in MV Infection. How do these observations reconcile the clinical descriptions of immunosuppression after MV infection and the primary role of DCs as stimulators of immune responses? One interesting possibility is that the giant multinucleated cells (Warthin-Finkeldy cells) in the submucosal areas of the tonsils and pharynx are syncytia consisting of DCs and T cells. The DCs that line the mucosal surfaces where there are also many T cells, are the most likely target cell candidates during viral transmission, as suggested for HIV-1 (21). DCs are an important component of the protective immune response to microbes. Strategically located (lungs, skin, gut, liver), DCs are also recruited into the airway epithelium during the inflammatory response to a broad spectrum of stimuli (22). Thus, DCs may be a reservoir for MV infection and a vehicle to transmit the virus to lymphoid cells in draining nodes. It remains to be seen whether DCs can also mediate protective immunity to MV.

DCs as APCs for Antiviral, T Cell–mediated Immunity

In murine systems, DCs were shown to be the most effective APCs for stimulating recall CTL responses to Sendai virus (23), Moloney leukemia virus (23), HSV (24), and influenza virus (25). However, these studies used viruses simply as antigens to illustrate the potency of DCs to induce $CD8^+$ CTL responses.

More recent analyses with human cells have monitored the viral life cycle in DCs. One example is influenza virus. Exposure of DCs to influenza virus at MOIs of 2–4 leads to >90% infection, as manifested by expression of the viral proteins HA and nonstructural protein 1 (26). The infection is nontoxic, as viral protein expression is sustained for >2 d with retention of viability. However, little infectious virus is produced. DCs also synthesize substantial amounts of IFN-α after infection, >3 ng/ml per 10^6 cells (Bender, A., M. Albert, A. Reddy, B. Sauter, G. Kaplan, W. Hellman, and N. Bhardwaj, manuscript submitted). Influenza infection of macrophages also results in viral protein expression in a majority of cells (70%), and synthesis of IFN-α. In contrast to DCs, however, macrophages begin to undergo apoptosis within 6–10 h, and most cells die within 24–36 h. During this interval macrophages synthesize low to moderate levels of virus (Bender, A., M. Albert, A. Reddy, B. Sauter, G. Kaplan, W. Hellman, and N. Bhardwaj, manuscript submitted).

Infected DCs, but not macrophages or B cells, can induce substantial recall CTL responses from purified blood $CD8^+$

T cells (26). Three pathways for presentation of influenza antigens to $CD8^+$ CTLs by DCs have been identified.

Infectious Virus. Relatively few DCs are required to generate CTL responses (stimulator/responder ratios of 1: 50–100) and low levels of infection (MOI of 0.02) are sufficient to generate potent CTLs (26). In contrast, infected monocytes are inactive in inducing these CTL responses, but can serve as targets for the CTLs that are induced by DCs.

Nonreplicating Virus. DCs pulsed with poorly replicating heat- or UV-inactivated influenza virus induce equally strong CTL responses to DCs pulsed with live virus (27). When pulsed with inactivated virus, <1% of DCs express viral protein, including nonstructural protein 1 (which is only synthesized in the infectious cycle), indicating that only small amounts of viral antigen are required by DCs to stimulate T cells (27). The binding and fusogenic functions of inactivated influenza virus are intact as assessed by standard hemagglutinating (binding) and hemolytic (fusion) assays. To be optimally effective, the inactivated virus must retain its fusogenic activity to presumably access the cytoplasm of DCs.

Virus-infected Apoptotic Cells. Monocytes and Hela cells undergo apoptosis after infection with influenza virus, and can be phagocytosed by uninfected DCs. It has now been shown that DCs process viral antigens from the apoptotic cells and acquire the capacity to induce virus-specific $CD8^+$ class I–restricted CTL responses (Albert, M., B. Sauter, and N. Bhardwaj, manuscript submitted). This pathway may account for the phenomenon of cross-priming in animal models, whereby antigens from donor cells could be presented by host bystander cells (28).

The role of DCs in stimulating influenza-specific responses may be physiologic since DCs are residents of airway epithelia and can be rapidly recruited here after exposure to pathogens (22).

DCs in Viral Pathogenesis

The HIV-1 system best illustrates the dual role of DCs during virus infection. DCs express the coreceptors required for the entry of HIV-1, that is, CD4 and several chemokine coreceptors like CXCR4 and CCR5 (29). When exposed to low levels of HIV-1, blood-derived DCs transmit a vigorous cytopathic infection to $CD4^+$ T cells which is characterized by syncytia formation, virion release, and T cell death by apoptosis (30–32). This is also the case for DCs derived from human skin (33).

There are three striking features of this system. First, DCs exposed to HIV-1 or carrying a relatively low level of proviral DNA, promote extensive viral replication upon interaction with syngeneic T cells in vitro (33, 34). Infectivity of mature DCs alone, either blood or skin, with HIV-1 is low, however, with few full-length reverse transcripts detectable after infection. After a pulse with MOI of 0.05–0.1, <100 copies of full-length transcripts are detected by PCR per 5×10^4 cells. This low level of infection persists for at least 5 d in vitro and is <10–100 fold less than seen with activated T cells (34). Second, infection in this DC–T cell system is independent of antigens or exogenous stimuli such as IL-2. Third, the syncytia that form are heterokaryons of DCs and T cells and are the sources of viral p24 and virion production. Eventually, cell death of the memory T cells ensues (33, 34).

Cells expressing HIV-1 gag proteins have been detected at the surfaces of mucosal lymphoid tissue, specifically the nasopharyngeal tonsil or adenoid. The cells are comprised of multinucleated syncytia expressing the S100 DC marker (21). Memory T cells traffic through extravascular spaces and can encounter tissue DCs in mucosal sites. Exposure to virus here would permit active replication when both cells interact with death of memory T cells. Thus, DCs may directly contribute to viral transmission, disease pathogenesis, and the high level of $CD4^+$ T cell death.

DCs could also have a role in eliciting $CD8^+$ anti–HIV-1 responses. Given the ability of DCs to present inactivated influenza virus or infected cells undergoing apoptosis (see above), it is possible that they might present defective HIV-1 (the majority of virus in plasma) or apoptotic $CD4^+$ T cells to $CD8^+$ T cells. So DCs at sites of viral replication may represent a double-edged sword, promoting HIV-1 replication and inducing antiviral resistance.

As Fugier-Vivier et al. point out (2), the effects of MV infection are curiously reminiscent of infection with HIV-1 where (*a*) only small amounts of virus are necessary to infect DCs (34), (*b*) low numbers of infected DCs induce extensive HIV-1 replication in cocultures of activated or memory T cells (33), possibly via CD40L (35), (*c*) apoptosis is induced in infected and bystander cells (15, 31), (*d*) there is reduced capacity to synthesize IL-12 (36), (*e*) syncytia form and are sites of extensive viral replication (30, 32, 33), and (*f*) virus-infected syncytia are prominent in the epithelium of oral lymphoid tissue (21).

The study of viral life cycles in APCs is leading to a new appreciation of the role of DCs in both protective and pathogenic aspects of viral infection. In influenza, new pathways for charging MHC class I molecules on DCs have been ascertained, in HIV-1 infection, routes for virus transmission have been identified, and in measles infection, new but still undefined pathways for immunosuppression have been discovered.

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References

1. Koup, R.A. 1994. Virus escape from CTL recognition. *J. Exp. Med.* 180:779–782.
2. Fugier-Vivier, I., C. Servet-Delprat, P. Rivailler, M.-C. Rissoan, Y.-J. Liu, and C. Rabourdin-Combe. 1997. Measles virus suppresses cell-mediated immunity by interfering with the survival and functions of dendritic and T cells. *J. Exp. Med.* 186:813–823.
3. Grosjean, I., C. Caux, C. Bella, I. Berger, F. Wild, J. Banchereau, and D. Kaiserlian. 1997. Measles virus infects human dendritic cells and blocks their allostimulatory properties for $CD4^+$ T cells. *J. Exp. Med.* 186:801–812.
4. Schnorr, J.-J., S. Xanthakos, P. Keikavoussi, E. Kampgen, V.T. Meulen, and S. Schneider-Schaulies. 1997. Induction of maturation of human blood dendritic cell precursors by measles virus is associated with immunosuppression. *Proc. Natl. Acad. Sci. USA.* 94:5326–5331.
5. Griffin, D.E., and W.J. Bellini. 1996. Measles virus. *In* Fields Virology. B.N. Fields, D.M. Knipe, and P.M. Howley, editors. Lippincott-Raven Publishers, Philadelphia. 1267–1312.
6. Dorig, R.E., A. Marcil, A. Chopra, and C.D. Richardson. 1993. The human CD46 molecule is a receptor for measles virus Edmonston strain. *Cell.* 75:295–305.
7. White, R., and J. Boyd. 1973. The effect of measles on the thymus and other lymphoid tissues. *Clin. Exp. Immunol.* 13: 343–357.
8. Beckford, A.P., R.O.C. Kaschula, and C. Stephen. 1985. Factors associated with fatal cases of measles: a retrospective autopsy study. *Afr. Med. J.* 68:858–863.
9. Arneborn, P., and G. Biberfeld. 1983. T-lymphocyte subpopulations in relation to immunosuppression in measles and varicella. *Infect. Immun.* 39:29–37.
10. Von Pirquet, C. 1908. Das verhalten der kutanen tuberkulinreaktion wahrend der masern. *Dtsch. Med. Wochenschr.* 34: 1297–1300.
11. McChesney, M.B., J.H. Kehrl, A.S. Valsamakis, A.S. Fauci, and M.B.A. Oldstone. 1987. Measles virus infection of B lymphocytes permits cellular activation but blocks progression through the cell cycle. *J. Virol.* 61:3441–3447.
12. McChesney, M.B., A. Altman, and M.B.A. Oldstone. 1988. Suppression of T lymphocytes function by measles virus is due to cell cycle arrest in G1. *J. Immunol.* 140:1269–1273.
13. McChesney, M.B., R.S. Fujinami, P.W. Lampert, and M.B.A. Oldstone. 1986. Viruses disrupt functions of human lymphocytes. II. Measles virus suppresses antibody production by acting on B lymphocytes. *J. Exp. Med.* 163:1331–1336.
14. Ward, B.J., and D.E. Griffin. 1993. Differential CD4 T-cell activation in measles. *J. Infect. Dis.* 168:275–281.
15. Badley, A.D., J.A. McElhinny, P.J. Leibson, D.H. Lynch, M.R. Alderson, and C.V. Paya. 1996. Upregulation of fas ligand expression by human immunodeficiency virus in human macrophages mediates apoptosis of uninfected T lymphocytes. *J. Virol.* 70:199–206.
16. Cella, M., D. Scheidegger, K. Palmer-Lehmann, P. Lane, A. Lanzavecchia, and G. Alber. 1996. Ligation of CD40 on dendritic cells triggers production of high levels of interleukin-12 and enhances T cell stimulatory capacity: T–T help via APC activation. *J. Exp. Med.* 184:747–752.
17. Koch, F., U. Stanzl, P. Jennewien, K. Janke, C. Heufler, E. Kampgen, N. Romani, and G. Schuler. 1996. High level IL-12 production by murine dendritic cells: upregulation via MHC class II and CD40 molecules and downregulation by IL-4 and IL-10. *J. Exp. Med.* 184:741–747.
18. Karp, C.L., M. Wysocka, L.M. Wahl, J.M. Ahearn, P.J. Cuomo, B. Sherry, G. Trinchieri, and D.E. Griffin. 1996. Mechanism of suppression of cell-mediated immunity by measles virus. *Science (Wash. DC).* 273:228–231.
19. Schlender, J., J.J. Schnorr, P. Spielhofer, T. Cathomen, R. Cattaneo, M.A. Billeter, V. terMeulen, and S. Schneider-Schaulies. 1996. Interaction of measles virus glycoproteins with the surface of uninfected peripheral blood lymphocytes induces immunosuppression in vitro. *Proc. Natl. Acad. Sci.* 93: 13194–13199.
20. Ravanel, K., C. Castelle, T. DeFrance, T.F. Wild, D. Charron, V. Lotteau, and C. Rabourdin-Combe. 1997. Measles virus nucleocapsid protein binds to FcγRII and inhibits human B cells antibody production. *J. Exp. Med.* 186:269–278.
21. Frankel, S.S., B.M. Wenig, A.P. Burke, P. Mannan, L.D.R. Thompson, S.L. Abbondanzo, A.M. Nelson, M. Pope, and R.M. Steinman. 1996. Replication of HIV-1 in dendritic cell-derived syncytia at the mucosal surface of the adenoid. *Science (Wash. DC).* 272:115–117.
22. McWilliam, A.S., S. Napoli, A.M. Marsh, F.L. Pemper, D.J. Nelson, C.L. Pimm, P.A. Stumbles, T.N.C. Wells, and P.G. Holt. 1996. Dendritic cells are recruited into the airway epithelium during the inflammatory response to a broad spectrum of stimuli. *J. Exp. Med.* 184:2429–2432.
23. Kast, W.M., C.J.P. Boog, B.O. Roep, A.C. Voordouw, and C.J.M. Melief. 1988. Failure or success in the restoration of virus-specific cytotoxic T lymphocyte response defects by dendritic cells. *J. Immunol.* 140:3186–3193.
24. Hengel, H., M. Lindner, H. Wagner, and K. Heeg. 1987. Frequency of herpes simplex virus-specific murine cytotoxic T lymphocyte precursors in mitogen- and antigen-driven primary in vitro T cell responses. *J. Immunol.* 139:4196–4202.
25. Nonacs, R., C. Humborg, J.P. Tam, and R.M. Steinman. 1992. Mechanisms of mouse spleen dendritic cell function in the generation of influenza-specific, cytolytic T lymphocytes. *J. Exp. Med.* 176:519–529.
26. Bhardwaj, N., A. Bender, N. Gonzalez, L.K. Bui, M.C. Garrett, and R.M. Steinman. 1994. Influenza virus–infected dendritic cells stimulate strong proliferative and cytolytic responses from human $CD8^+$ T cells. *J. Clin. Invest.* 94:797–807.
27. Bender, A., L.K. Bui, M.A.V. Feldman, M. Larsson, and N. Bhardwaj. 1995. Inactivated influenza virus, when presented on dendritic cells, elicits human $CD8^+$ cytolytic T cell responses. *J. Exp. Med.* 182:1663–1671.
28. Bevan, M.J. 1976. Cross-priming for a secondary cytotoxic response to minor H antigens with H-2 congenic cells which do not cross-react in the cytotoxic assay. *J. Exp. Med.* 143: 1283–1288.
29. Granelli-Piperno, A., B. Moser, M. Pope, D. Chen, Y. Wei, F. Isdell, F. O'Doherty, W. Paxton, R. Koup, S. Mojsov, et al. 1996. Efficient interaction of HIV-1 with purified dendritic cells via multiple chemokine coreceptors. *J. Exp. Med.* 184:2433–2438.
30. Cameron, P.U., P.S. Freudenthal, J.M. Barker, S. Gezelter, K. Inaba, and R.M. Steinman. 1992. Dendritic cells exposed to human immunodeficiency virus type-1 transmit a vigorous cytopathic infection to CD4+ T cells. *Science (Wash. DC).* 257:383–387.
31. Cameron, P.U., M. Pope, S. Gezelter, and R.M. Steinman. 1994. Infection and apoptotic cell death of CD4+ T cells during an immune response to HIV-1 pulsed dendritic cells.

AIDS Res. Hum. Retroviruses. 10:61–71.
32. Cameron, P., M. Pope, A. Granelli-Piperno, and R.M. Steinman. 1996. Dendritic cells and the replication of HIV-1. *J. Leukocyte Biol.* 59:158–171.
33. Pope, M., M.G.H. Betjes, N. Romani, H. Hirmand, P.U. Cameron, L. Hoffman, S. Gezelter, G. Schuler, and R.M. Steinman. 1994. Conjugates of dendritic cells and memory T lymphocytes from skin facilitate productive infection with HIV-1. *Cell.* 78:389–398.
34. Pope, M., S. Gezelter, N. Gallo, L. Hoffman, and R.M. Steinman. 1995. Low levels of HIV-1 in cutaneous dendritic cells initiate a productive infection upon binding to memory $CD4^+$ T cells. *J. Exp. Med.* 182:2045–2056.
35. Pinchuk, L.M., P.S. Polacino, M.B. Agy, S.J. Klaus, and E.A. Clark. 1994. The role of CD40 and CD80 accessory cell molecules in dendritic cell–dependent HIV-1 infection. *Immunity.* 1:317–325.
36. Chehimi, J., S.E. Starr, I. Frank, A. D'Andrea, X. Ma, R.R. Macgregor, J. Sennelier, and G. Trinchieri. 1994. Impaired interleukin-12 production in human immunodeficieny virus–infected patients. *J. Exp. Med.* 179:1361–1366.